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AFIOH

DoD Global Influenza Surveillance Program Season Summary: October 2004 – April 2005

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13. ABSTRACT *(Maximum 200 words)*

The U.S. Air Force Institute for Operational Health (AFIOH) manages the worldwide sentinel site component of the DoD Global Influenza Surveillance Program. AFIOH conducts influenza surveillance among 32 U.S. Air Force, Army, Navy, and Coast Guard sentinel site installations around the world and also processes specimens from DoD overseas research laboratories and non-sentinel sites. During the 2004-2005 influenza season (3 October 2004 to 30 April 2005), the AFIOH laboratory processed 2,772 specimens. Of these, 906 (33%) were positive for influenza. Eighty-one percent (n=735) of influenza isolates were influenza A and 19% (n=171) were influenza B. Five hundred thirty-two (72%) of the influenza A isolates were subtyped, all of which were H3N2. One hundred ten (64%) of the influenza B isolates were subtyped; 94 were subtyped as B/Sichuan-like and 16 were B/Hong Kong. Most of the A/H3N2 isolates analyzed by sequence analysis were analogous to A/California-like viruses and thus have evolved from the A/Fujian (Wyoming) vaccine strain. Influenza A predominated at European, North American, South American and deployed sites, accounting for 79% to 100% of influenza isolates in these areas. In contrast, nearly half of isolates from Asian/Pacific sites were influenza B.

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DOD GLOBAL INFLUENZA SURVEILLANCE PROGRAM
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SEASON SUMMARY: OCTOBER 2004–APRIL 2005

INTRODUCTION

Influenza poses a significant threat to military readiness. This threat was first recognized during the 1918 influenza pandemic, which took the lives of 43,000 US military personnel[1]. More recent outbreaks have underscored the continued effects on military training and operational missions. In an effort to monitor and prevent outbreaks of influenza attributable to newly emerging strains, the US Air Force has conducted global influenza surveillance on US military forces and their families since 1976. In 1997, the Office of the Assistant Secretary of Defense for Health Affairs named the Air Force Surgeon General the Executive Agent for the Department of Defense (DoD) Influenza Surveillance, thus expanding influenza surveillance from an Air Force program to one that is DoD wide. The tri-service program is largely funded by the DoD Global Emerging Infections Surveillance and Response System (DoD-GEIS).

The DoD Global Influenza Surveillance Program includes sentinel site surveillance (managed by the Air Force Institute for Operational Health [AFIOH]), population-based surveillance (managed by the Naval Health Research Center [NHRC]), and DoD overseas research laboratories. Two overseas laboratories, Naval Medical Research Center Detachment (NMRC-D) in Lima, Peru, and the Armed Forces Research Institute for Medical Sciences (AFRIMS) in Bangkok, Thailand, participate in the AFIOH sentinel site program. Additionally, Naval Medical Research Unit No. 2 (NAMRU-2) in Jakarta, Indonesia, and Naval Medical Research Unit No. 3 (NAMRU-3) in Cairo, Egypt, conduct influenza surveillance with the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC).

This report summarizes AFIOH activities during the 2004-05 season. Refer to Appendix A for 2004-05 season summaries from NHRC and overseas research laboratories in Indonesia and Egypt.

METHODS

Surveillance Populations

The US Air Force manages the worldwide sentinel site component of the DoD Global Influenza Surveillance Program, which can further be divided into active and passive surveillance sections.

Thirty-two US Air Force, Army, Navy, and Coast Guard installations around the world are currently recognized as sentinel sites (refer to Table B1 for a list of sentinel sites). Sentinel site selections are reviewed annually using the principal criteria of military mission and geographic location, with an additional criterion of past performance with specimen submission. Traditionally, military training sites, international military ports, and overseas installations have been chosen as sentinel sites. In addition, deployed locations are now an important focus for sentinel site selection, focusing on CENTCOM in particular. Sentinel site specimens are generally obtained from active duty (AD) military members and their dependents. Public Health Officers (PHOs) are actively contacted on a yearly basis to encourage participation in the program; PHOs subsequently encourage base health care providers to collect specimens for submission to AFIOH. Hence, sentinel sites fall under the active surveillance section of the AFIOH program.

Additionally, active surveillance is performed by DoD overseas research laboratories in Central and South America via NMRC-D and in Thailand and Nepal through AFRIMS. Principal investigators at the laboratories work with AFIOH personnel to ensure IRB-approved research protocols are in place to conduct surveillance. Overseas laboratory specimens are obtained from local populations rather than AD members and dependents. Specimens are often collected over longer periods of time and sent to AFIOH in batches throughout the season.

Finally, since AFIOH serves as the central reference laboratory for the Air Force and other tri-service sites, non-sentinel sites submit specimens on a voluntary or as-needed basis. Specimens from non-sentinel sites are obtained from AD members and their dependents. Often, results obtained from these specimens are clinically relevant to submitting sites. Since submission by non-sentinel sites is done on an as-needed clinical basis, this section of the program is classified as passive surveillance.

Data from sentinel, non-sentinel, and overseas laboratory sites will be summarized overall and also separately, where appropriate, due to differences in sample collection strategies outlined above. Stratification by site categories will allow data to be presented in the most accurate manner possible.

Specimen Collection, Processing and Characterization

Site health care providers collect nasal washes or nasal/throat swabs, as appropriate, from individuals presenting with a fever and either a cough or sore throat. Specimens are sent to the AFIOH Epidemiology Surveillance Division laboratory at Brooks City-Base, Texas, for viral isolation and identification. Sentinel sites are requested to submit 6 to 10 specimens per week during the Northern Hemisphere influenza season (October - April), although specimens are accepted throughout the year. If there are fewer than 6 cases meeting the case definition, sites are encouraged to submit only those that satisfy the case definition. Tripler AMC and Landstuhl RMC submit only positive influenza specimens for subtyping; the initial cultures are performed in their laboratories.

When received by AFIOH, specimens are cultured and examined for the presence of respiratory viruses including influenza A and B, adenovirus; parainfluenza virus, enterovirus, respiratory syncytial virus (RSV), and herpes simplex virus (HSV). All influenza isolates are typed; those from overseas installations and a representative sample from domestic installations are also subtyped.

Selected influenza isolates also undergo molecular characterization. Genetic sequencing of the hemagglutinin surface proteins is performed to detect variations from the vaccine component strains. Results are shared with the CDC. Information from the molecular characterizations and overall world surveillance are presented each year to the US Food and Drug Administration Vaccines and Related Biological Products Advisory Committee (VRBPAC), which recommends modifications to the influenza vaccine based on the viral strains that circulated during the preceding season.

Data Reporting

The data generated by this program are particularly important for two additional reasons. First, program specimens are received from areas of the world where novel influenza strains have historically emerged. Second, the DoD program has made possible influenza surveillance in geographic regions where very little is known about influenza activity.

The AFIOH laboratory sends clinical results back to the submitting laboratory as a patient report and to the AFIOH Epidemiology Services Branch, which notifies each installation's public health/preventive medicine office of confirmed influenza cases. Additionally, the AFIOH Epidemiology Services Branch summarizes weekly surveillance data in a report describing influenza activity within the DoD, the US, and throughout the world. This weekly update is distributed to all participating sites, the CDC, the Texas Department of State Health Services, and to other interested DoD parties. Weekly reports are posted on the AFIOH influenza website: https://gumbo.brooks.af.mil/pestilence/Influenza/

RESULTS AND DISCUSSION

Overall Summary

During the 2004–05 influenza season (3 October 2004 to 30 April 2005), the AFIOH laboratory processed 2,772 specimens from sentinel, non-sentinel, and overseas laboratory sites. Of these, 906 (33%) were positive for influenza. Specimens were received from 31 of 32 sentinel sites, 1 overseas laboratory, and 43 non-sentinel sites worldwide. Of the 2,772 specimens, 65% (n=1,809) were received from sentinel sites.

**Of note, data incompleteness is an important limitation of this year's surveillance results due to low participation levels by many sentinel sites. A major goal in preparing for next year's season is to explore ways to encourage and standardize sentinel site participation in order to obtain a more complete picture of influenza activity within DoD.

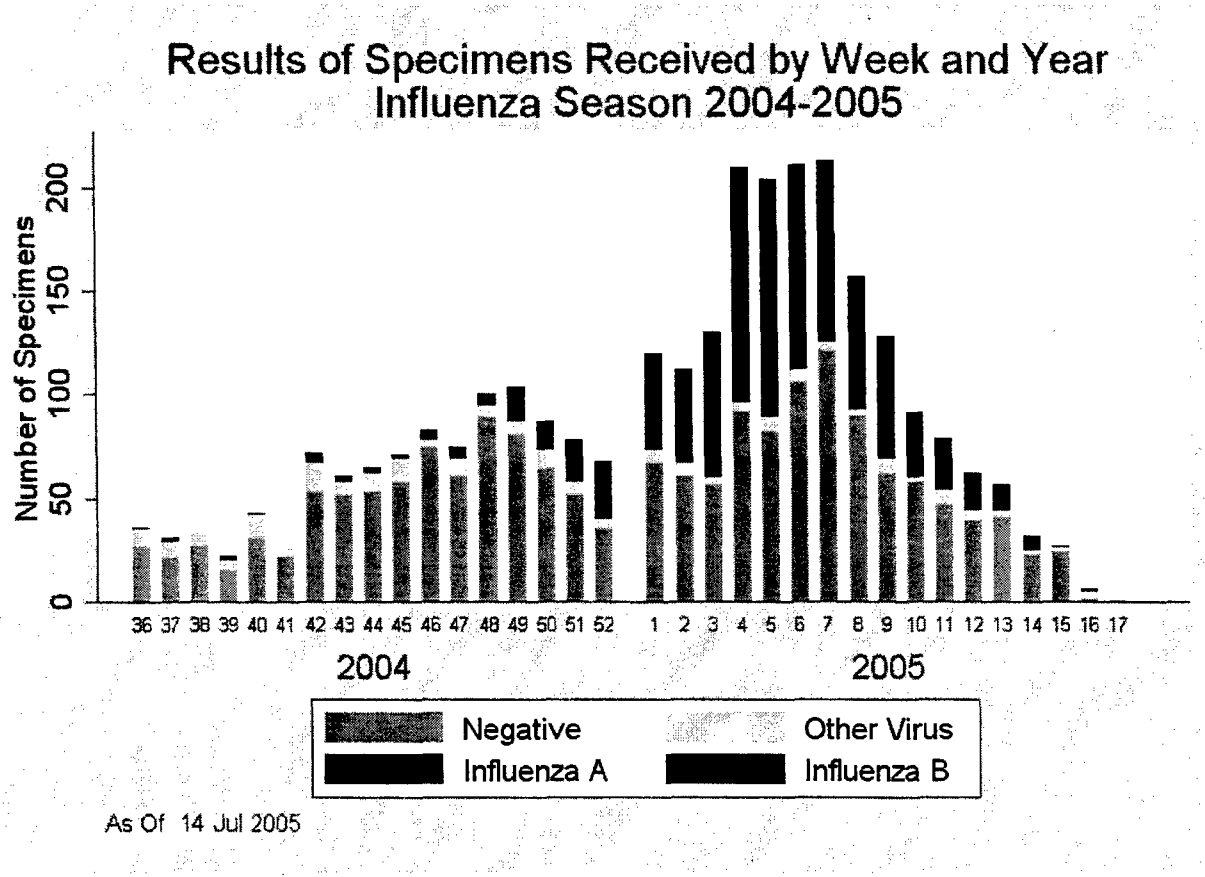

Figure 1. DoD Laboratory-based Influenza Surveillance Summary, 2004-05 Season

Respiratory Isolates

Of the 2,772 total specimens, 1,076 (39%) specimens were positive for respiratory viruses. Sixty-eight percent (n=735) of the isolates were influenza A, and 16% (n=171) were influenza B. Nine percent (n=97) were adenovirus (Figure 2); the majority of adenovirus specimens were collected from Lackland Air Force Base (AFB), Texas (n=25) and Scott AFB, Illinois (n=26). The remaining 7% (n=73) of respiratory isolates were one of the following: HSV (n=32), parainfluenza virus (n=26), enterovirus (n=10), or RSV (n=5).

Respiratory viruses were isolated from specimens collected at all 31 submitting sentinel sites. Of the 1,809 specimens from sentinel sites, 749 (41%) specimens were positive for respiratory viruses. Seventy-one percent (n=531) of the isolates were influenza A, 18% (n=136) were influenza B; 7% (n=50) were adenovirus. HSV (n=13), parainfluenza virus (n=13), enterovirus (n=4), and RSV (n=2) comprised the remaining 4% of isolates.

Table summaries of all specimens from sentinel, non-sentinel, and overseas laboratory sites are located in Table B2.

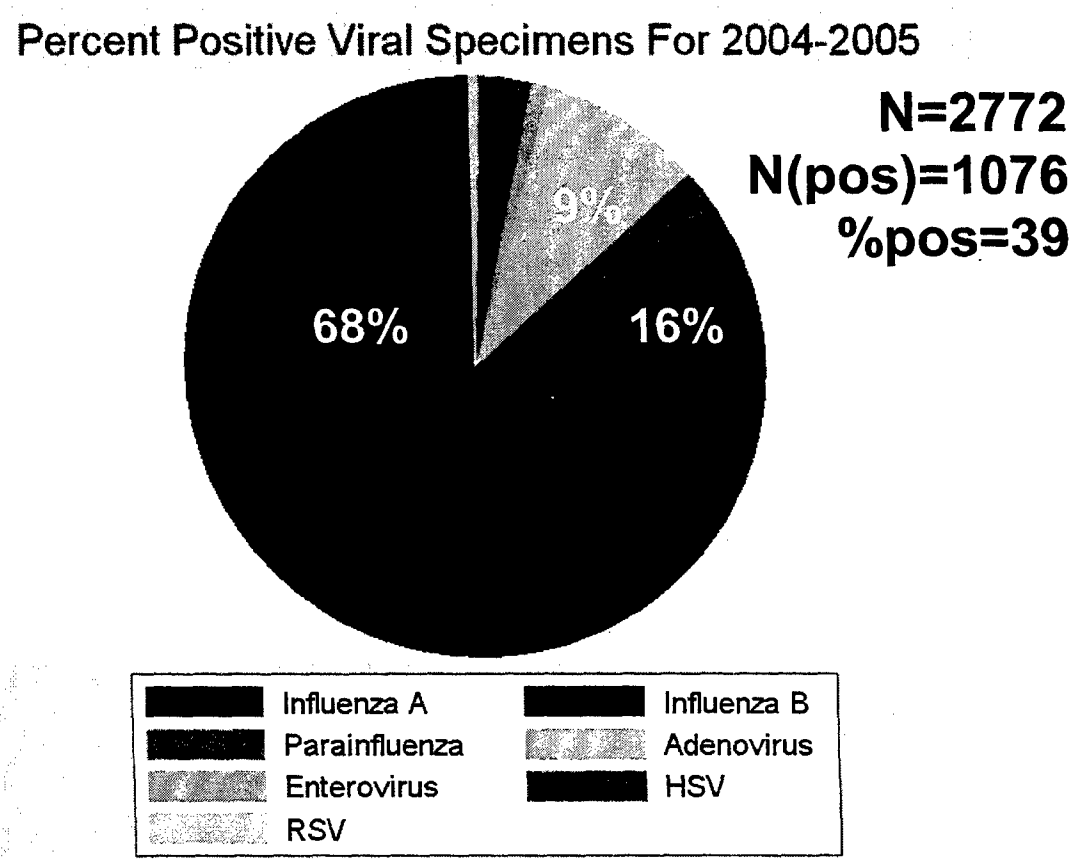

Figure 2. Distribution of Positive Respiratory Viruses, 2004-05 Season

Influenza Isolates

Of the 906 influenza isolates from all sites, 81% (n=735) were influenza A and 19% (n=171) were influenza B (Influenza A to influenza B ratio of 4.3:1). This is dramatically different from last year where influenza B made up less than 1% of all influenza isolates. This finding is consistent with the CDC surveillance program, which reported an influenza A to influenza B ratio of 3:1 this year[2].

Influenza A activity peaked (measured by the proportion of influenza positives from all specimens) in Week 3 (16–22 Jan 2005), with 53% (n=69) of specimens positive for influenza A. Influenza B activity peaked in Week 9 (27 Feb–5 Mar 2005), with 16% (n=21) of specimens positive for influenza B. National influenza surveillance data from the CDC show a similar overall peak at Week 6[2].

Influenza A isolates were collected from 25 of 31 submitting sentinel sites and influenza B isolates were collected from 14 sentinel sites. Of the 668 influenza isolates from sentinel sites, 79% (n=531) were influenza A and 21% (n=137) were influenza B (Influenza A to influenza B ratio of 3.9:1).

Table summaries of positive influenza specimens from sentinel, non-sentinel, and overseas laboratory sites are located in Table B3.

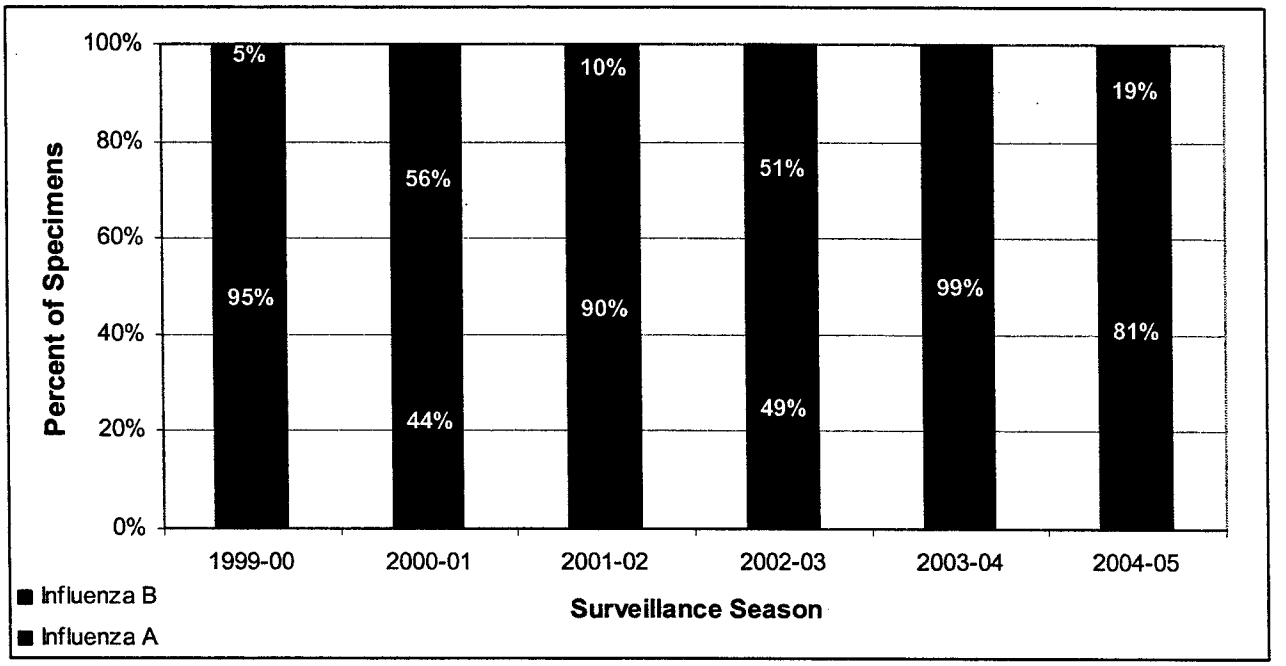

Figure 3. Influenza Isolates by Type and Season, 1999-2005

Molecular Analysis of Isolates

Five hundred thirty-two (72%) of the influenza A isolates were subtyped, all of which were H3N2. One hundred ten (64%) of influenza B isolates were subtyped; 94 were subtyped as B/Sichuan-like and 16 were B/Hong Kong. Figure 4 shows the proportion of influenza A to influenza B isolates for the past five seasons.

Further characterization via direct DNA sequencing of the hemagglutinin genes from more than 250 influenza A and B isolates was performed and compared with human vaccine component strains. Thorough genetic characterization is necessary to determine the level of homology to vaccine and reference strains since specific amino acid substitutions, i.e., mutations at or near antibody combining or receptor binding sites can affect vaccine efficacy, receptor specificity, and viral pathogenesis. Furthermore, molecular epidemiology using sequence analysis is essential for effectively tracking and monitoring (at the genetic level) the global spread of influenza field isolates obtained from the 35+ worldwide DoD influenza sentinel sites.

The majority of the AFIOH isolates analyzed by sequence analysis contained the signature amino acid substitutions observed in the A/California-like viruses and thus have evolved from the last year's H3N2 A/Fujian (Wyoming) vaccine strain. Compared to A/Fujian/411/02, strains sequenced in 2004/05 contained amino acid changes in positions distributed over antigenic sites A, B and D. The major sublineage change was noted at position 145 (K145N) located adjacent to antibody binding site A. Additional novel changes included 189 (S189N) in antibody binding site B and 226 (V226I) and 227 (S227P) located in antigenic site D. The A/California/7/04 isolate, selected for the 2005-2006 vaccine strain contains all of the residues observed in DOD-GEIS isolates at the above-mentioned positions.

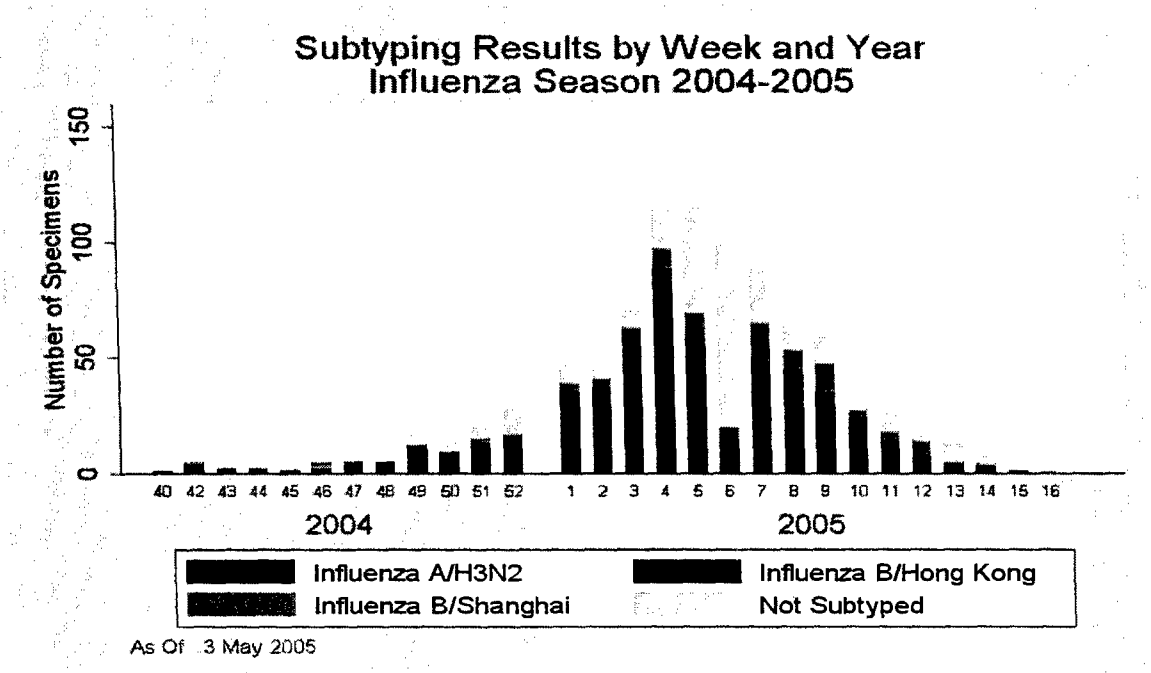

Figure 4. Summary of Subtyping Results*, 2004-05 Season

* Subtyping of samples declined in weeks 5-7 due to the heavy workload of the AFIOH laboratory during the flu season's peak. Influenza subtyping is generally performed as the schedule allows.

Geographic Distribution of Isolates

Influenza Isolates

During the 2004-05 season, early influenza isolates were obtained from Alaska and the US east coast, and were primarily type A (insufficient number of specimens to determine when peak activity occurred). Peak influenza activity occurred in early 2005 at European and the continental US sites and slightly later in the Asia/Pacific region (Figures 5a, 5b, and 5c). Generally, influenza A was isolated early on, followed by a larger proportion of influenza B later in the season. For South American sites, time of peak influenza activity was not determined due to seasonal differences from the northern hemisphere and the wide variety of climates and altitudes between the sites. Peak activity at deployed sites was also not determined due to low specimen numbers resulting from the difficulty in collecting samples during wartime conditions.

Influenza A predominated at European, North American, South American and deployed sites, accounting for 79% to 100% of influenza isolates in these areas (Figure 6). In contrast, nearly half of isolates from Asian/Pacific sites were influenza B.

Geographic data are presented in aggregate format rather than separately by site type to gain the most complete picture of global influenza activities in 2004-05. Table summaries of all specimens by continent/region are located in Table B4.

Molecular Analysis

Influenza A/H3N2 was collected from all participating sites and was the only influenza A subtype identified during the 2004-05 season. Regarding influenza B, the Shanghai strain predominated and was found in all locations where influenza B was collected. In contrast, influenza B/Hong Kong was only collected in a few locations: Georgia, Hawaii, and South America, though Shanghai was the predominant strain in these locations as well.

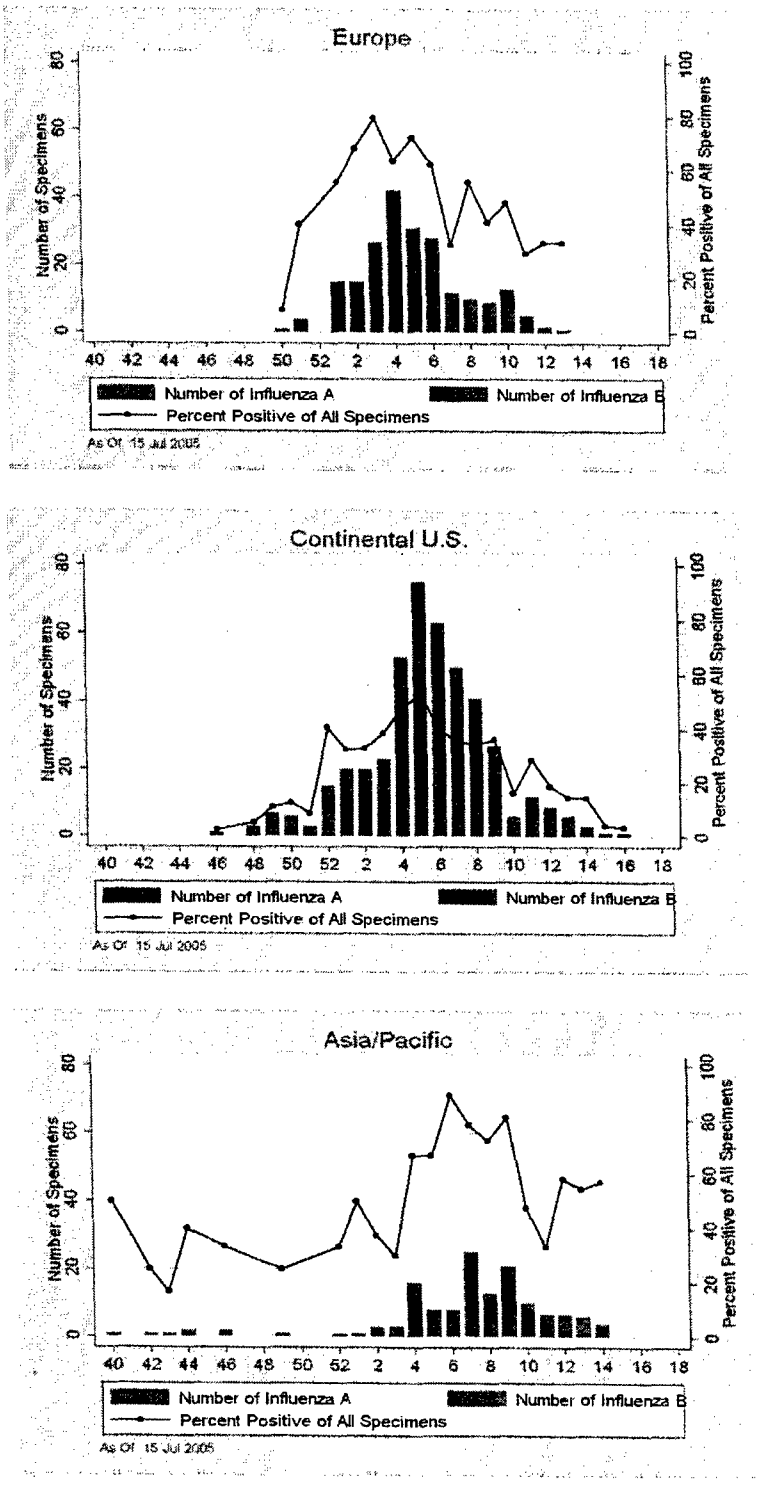

Figure 5. Percent and Total Number Influenza Positive Specimens*† by Type and Continent, 2004-05 Season

* Hawaii was added to Asia/Pacific due to its location in the Pacific

† Tripler AMC, Hawaii, and Landstuhl RMC, Germany, were excluded from above figures since only positive influenza specimens are received from these locations

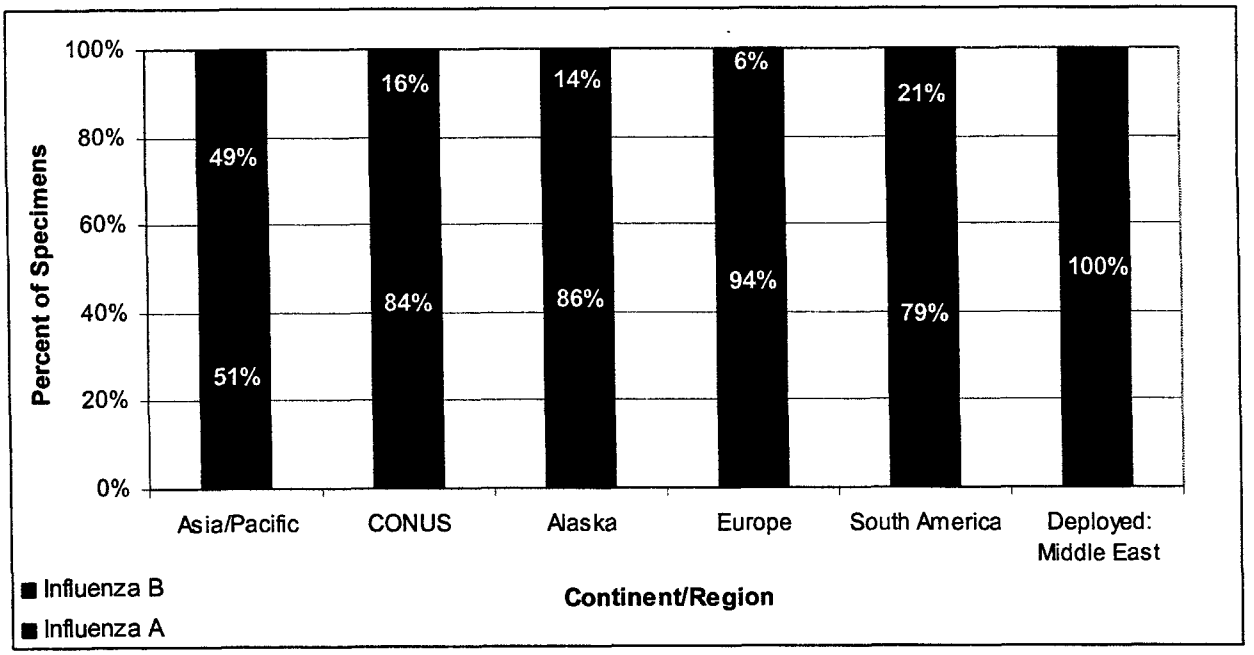

Figure 6. Influenza Isolates by Type and Geographic Region, 2004-05 Season

Demographics - Age Group

Patient age data were available for 92% of all samples. Patient ages ranged from less than 1 year to 90 years, with a median age of 21 years, reflecting the generally youthful population. The median age of service members (active duty or retirees) was 27, while the median age of non-service members was 9. Figure 7 summarizes these findings by age group.

Age data are presented in aggregate format rather than separately by site type to gain the most complete picture of persons affected by influenza in 2004-05. Table summaries of all specimens by age group are located in Table B5.

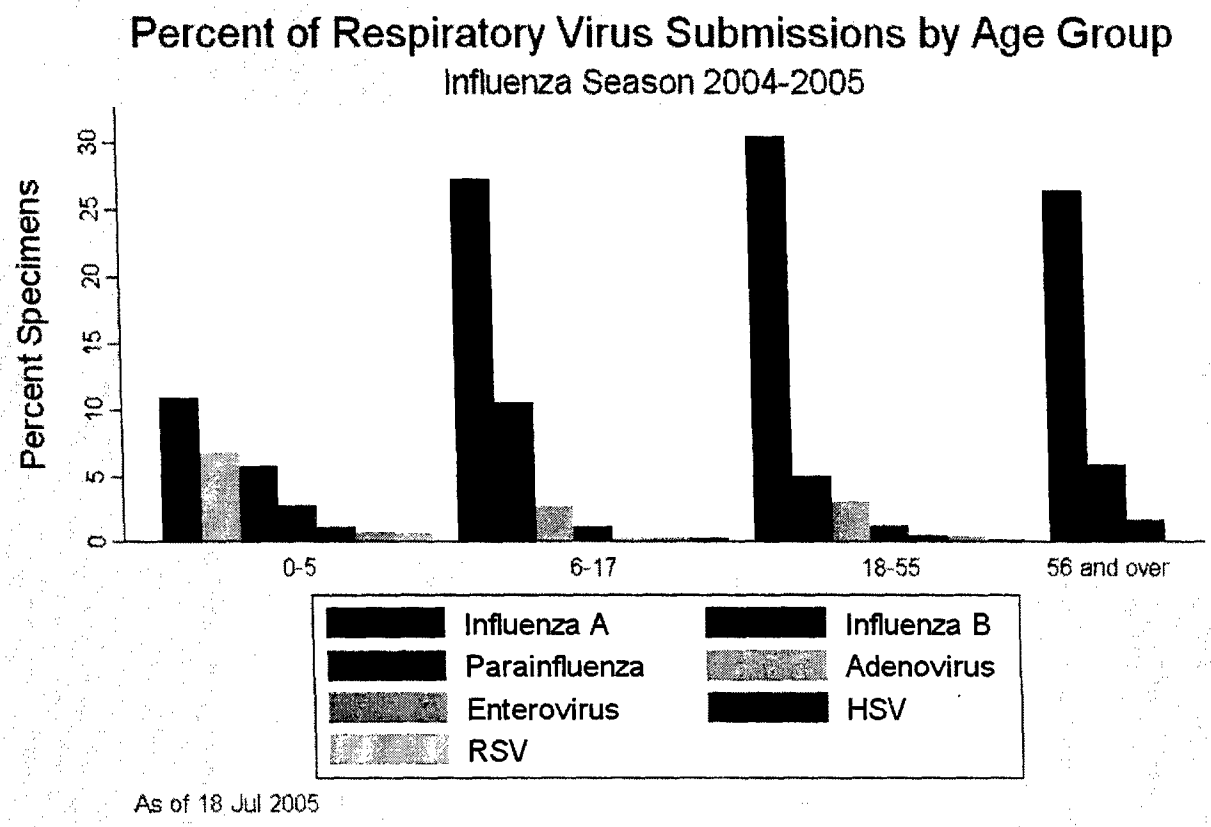

Figure 7. Respiratory Virus Isolates by Type and Age Group, 2004-05 Season

Demographics - Military Status

Family member prefix (FMP) information was available for 87% of specimens. Of these, 1,231 (44%) were classified as service members (active duty and retirees), 1,181 (42%) were classified as family members or dependents, and 21 (1%) was classified as "Other". Persons categorized as "Other" included civilians and other qualified beneficiaries. The 13% of specimens with missing FMP information were from non-military members submitted by the overseas research labs (NMRC-D). Figure 8 summarizes the isolate findings by military status.

Military status data are presented in aggregate format rather than separately by site type to gain the most complete picture of persons affected by influenza in 2004-05. Table summaries of all specimens by FMP are located in Table B6.

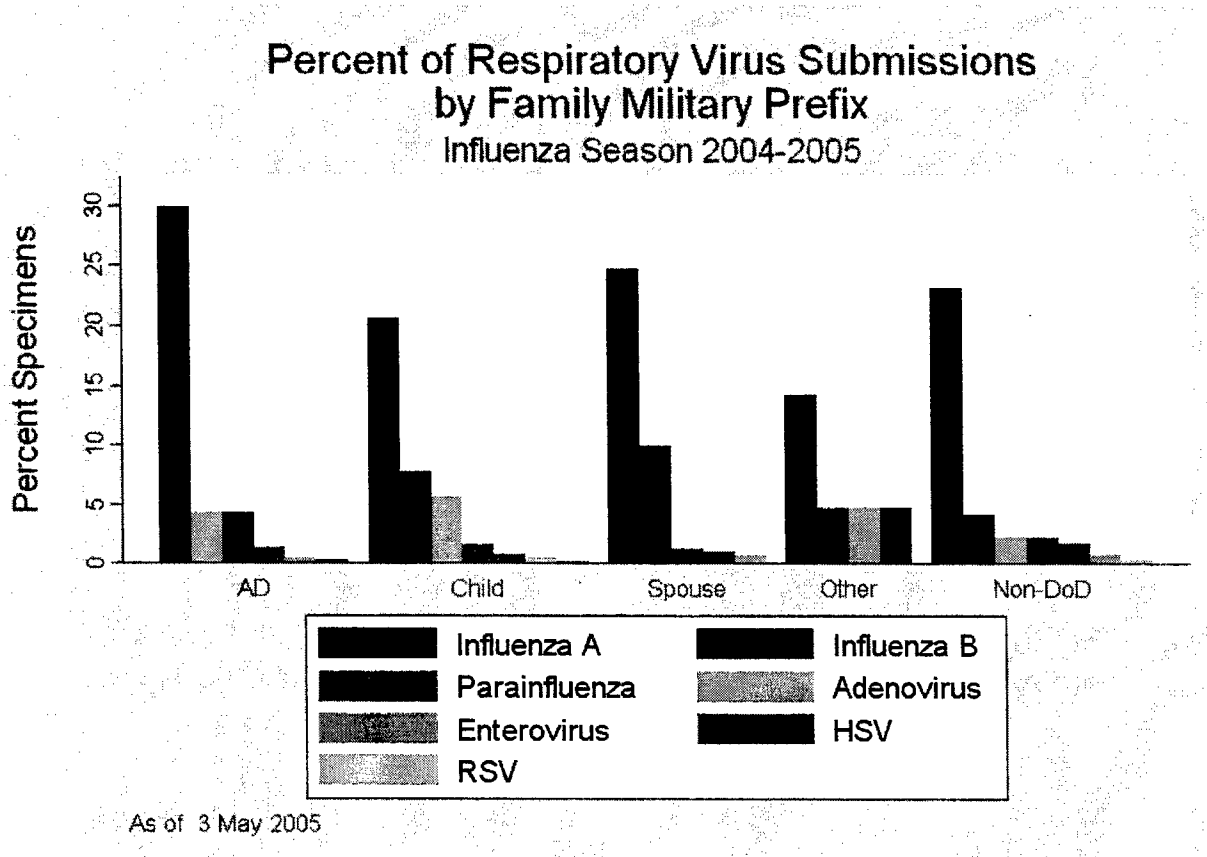

Figure 8. Respiratory Virus Isolates by Type and Military Status, 2004-05 Season

Influenza-like Illness

During the 2004-05 season, the average proportion of visits for influenza-like illness (ILI) in primary care clinics and emergency departments throughout the Global Military Health System was 10.1%. The DoD data was compiled through the Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE). The influenza-like illness category in ESSENCE is comprised of 28 International Classification of Diseases, Version 9 (ICD-9) codes that are thought to be most associated with ILI in primary care and emergency department settings. Estimates of completed records run between 70 and 90% outpatient encounters in the DoD that are entered by the patient's provider[3]. The proportion of ILI visits derived from ESSENCE is not comparable to the proportion of ILI visits in the CDC weekly influenza reports, because the latter uses symptomatic criteria, not ICD-9 coding, to define an ILI visit.

Figure 9 compares this season's overall ILI trends to the 2002-03 and 2003-04 influenza seasons.

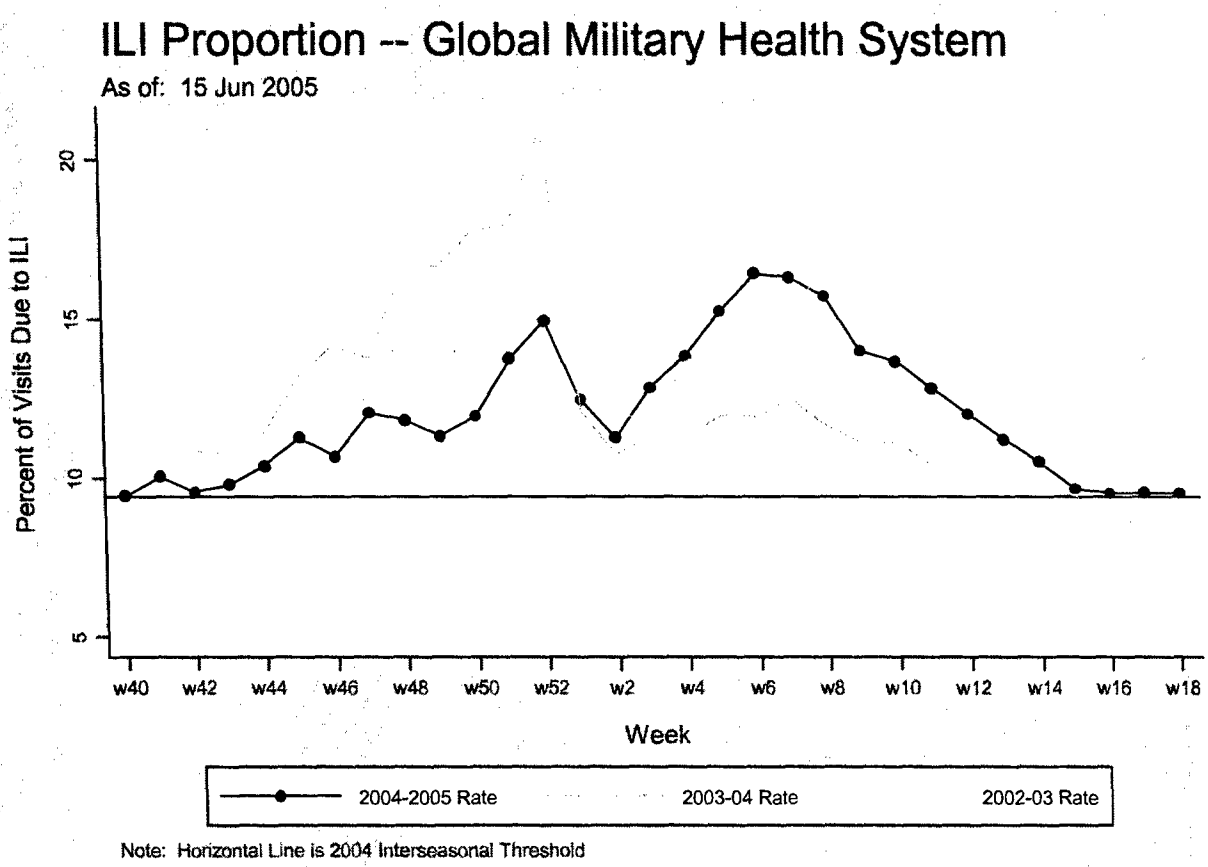

Figure 9. Percentage of ILI Visits, Global Military Health System

Vaccination Status

The vaccination status of Air Force influenza patients was assessed through the Air Force Complete Immunizations Tracking Application (AFCITA), formerly the Military Immunization Tracking System (MITS). During the 2004-05 season, only 10% (93) of the 906 active duty Air Force members (ADAF) and their dependents who were positive for influenza had an influenza vaccination record at least 2 weeks prior to the date of collection of their respiratory specimen. In comparison, during the 2003-04 season, of all patients who had a positive influenza specimen, approximately 21% had been vaccinated 14 or more days prior to the time of specimen collection. The most likely explanation for this difference was the 2004-2005 influenza vaccine shortage.

Review of Surveillance Questionnaires

While all specimens are processed regardless of whether they meet the case definition (either radiological evidence of viral pneumonia or temperature ≥100.5°F and cough or sore throat), submissions that do so are more likely to have a positive diagnosis, provided they are submitted within 3 days of symptom onset. MTF providers are given standard surveillance questionnaires to be submitted along with specimens; these can be utilized to examine submission guideline adherence.

Of 2,772 samples submitted, 350 (12.6%) were accompanied by a surveillance questionnaire. Of the 274 questionnaires that recorded clinical information, 233 (85%) met the case definition. For the 320 questionnaires in which both time of symptom onset and visit were recorded, 247 (77%) of the patients were seen within the first three days (presumably a throat swab was taken when the patient was seen). Overall, providers who submitted questionnaires seemed to reasonably follow sample submission guidelines, though submission guideline adherence could not be assessed for 87.4% of submitted specimens.

SPECIAL STUDIES

Vaccine Effectiveness

One hundred twenty-seven Air Force active duty sponsors of individuals who had a positive influenza isolate were interviewed regarding the vaccination and ILI status of household contacts of the primary case. Complete data were obtained for 376 household contacts. Excluding index cases, the secondary ILI attack rate among 15 vaccinated contacts was 0.246, compared to 0.251 among 71 unvaccinated contacts. The crude vaccine effectiveness against secondary ILI was 2%. Including *all* data (index cases and contact), the study found an ILI attack rate of 0.36 among 28 vaccinated persons, compared to an ILI attack rate of 0.41 among 164 unvaccinated persons. The crude vaccine effectiveness against ILI was 12%.

Information was gathered on more persons this year than last (376 contacts enrolled as compared to 175 last year). However, one important limitation of this year's study was that only 42% (127 of 299) of eligible active duty sponsors were enrolled, mainly due to difficulty reaching sponsors, AFIOH staffing limitations, and deployments.

Delays in vaccine distribution may have contributed to the extremely low effectiveness rate found, as 84 (52%) of 161 subjects with known vaccination dates received the vaccine after becoming ill or being exposed to an ill family member. By February, only 80% of ADAF had received the vaccine, and many household contacts were not vaccinated at all this year. As a result, we cannot determine the extent of protection offered by the current vaccine against the predominant circulating influenza strains this year, though it is evident that early vaccination is likely very important.

ACCOMPLISHMENTS

New Sentinel Sites Added

Five new sentinel sites were added this season: Scott AFB, Illinois; Landstuhl RMC, Germany; Balad AB, Iraq; NH, Guam; and BMC Sasebo, Japan. The DoD Influenza Surveillance Program staff annually evaluates the potential surveillance utility of military bases from all services and seeks sentinel site participation from new sites located in strategic areas of the world.

Nepal Outbreak

In late June 2004, AFRIMS was informed of an outbreak of Influenza-Like Illness (ILI) at a Bhutanese Refugee camp in East Nepal. Because AFRIMS had a satellite field site in Katmandu, they were able to send personnel to do an on-site investigation. AFRIMS personnel collected specimens from hospitalized patients who met the ILI case definition on 1-3 July. Sixty-four specimens were routed to the main AFRIMS facility in Bangkok, and were subsequently sent to the AFIOH laboratory in San Antonio within one week. Testing by the AFIOH laboratory found that 42/62 samples were positive for influenza A/H3N2, thus ruling out the possibility the outbreak was due to avian influenza.

There were four major amino acid differences observed within these isolates, three of which were located within antibody combining sites. The lineage specific molecular distinction observed within these genetic variants was a K140N amino acid substitution. The genetically similar A/California/4/2004 was recently selected as the 2005-06 H3N2 influenza vaccine strain. All four of the mutations observed in isolates from the outbreak in Nepal are present within the A/California/4/2004 variant. The early detection of these variant strains highlights the importance of continued real-time genetic characterization of field isolates. Since the Nepal isolates were first characterized, the majority of strains from both the US and abroad have contained the signature amino acid sequences observed within the A/Nepal strains.

This example illustrates the worldwide reach of the DoD Global Influenza Surveillance Program, including places not well covered by other surveillance networks, such as Nepal and Peru. Our extensive network allows us to detect influenza outbreaks in many parts of the world, as well as rule out the possibility of avian influenza as needed. Molecular sequencing of received isolates can play an important part in recommendations by the CDC and WHO as to future vaccine compositions in both the Northern and Southern Hemispheres, as shown in this example. Finally, this example illustrates the importance of our partnerships both with overseas DoD installations such as AFRIMS and NMRC-D, as well as with civilian agencies like the CDC.

Laboratory Training Visit to AFRIMS, Bangkok, Thailand

In May 2005, Mr. Luke T. Daum, a molecular biologist from the AFIOH laboratory, traveled to the Armed Forces Research Institute for Medical Sciences (AFRIMS) in Bangkok, Thailand. The purpose of the trip was to provide training, guidance, and instruction to laboratory personnel for the molecular detection of influenza viruses using real-time PCR assays developed at AFIOH. AFRIMS is a clinical diagnostic and research laboratory that serves the United States Armed Forces in Southeast Asia. On behalf of AFIOH, Mr. Daum provided technical protocols, influenza RT-PCR assays, and the reagents and consumables necessary for extraction and detection of influenza from clinical specimens using real-time RT-PCR. AFIOH and AFRIMS will continue to collaborate in an effort to evaluate original clinical specimens using influenza RT-PCR probes. AFIOH is developing other influenza subtype specific assays, and future collaboration in viral detection and molecular epidemiology between AFIOH and AFRIMS is anticipated.

Influenza RT-PCR Probe Development

AFIOH has developed 3 influenza fluorogenic RT-PCR probe sets for the rapid detection of influenza viruses from clinical isolates. These probe sets were funded by GEIS and have been designed, developed, and validated by the AFIOH laboratory. Two probes are type specific, capable of detecting influenza A or B. The third probe is subtype specific and targets H5 influenza. Two other human influenza

H3 and H1 subtype specific probes are currently being designed, tested, and evaluated in clinical isolates at AFIOH. All AFIOH probes will be tested and validated in collaboration with AFRIMS during the 2005-06 season.

Epidemic Outbreak Surveillance Program Support

GEIS funding has assisted in the efforts of the Epidemic Outbreak Surveillance (EOS) program. EOS is a consortium of DoD laboratories devoted to the development of a clinical respiratory microarray pathogen chip. Mr. Luke Daum at AFIOH has offered professional consultation and expertise in the design of the influenza portion of the EOS pathogen chip. Several hundred influenza hemagglutinin sequences obtained through the GEIS program at AFIOH were shared with EOS to assist in molecular detection of influenza from microarray chip analysis. Additionally, DNA sequencing of several influenza isolates for comparison to the chip data was also performed through the GEIS influenza program at AFIOH.

Epidemiologic Influenza Surveillance Assistance Visit to NAMRU-3, Cairo, Egypt

Lt Col Philip Gould, Preventive Medicine Consultant at AFIOH, was invited to serve as a guest Epidemiologist at NAMRU-3 in Cairo, Egypt, from 7 February to 20 April 2005.

Objectives for the visit included:

- Assisting in the development of the World Health Organization/Eastern Mediterranean Regional Office influenza surveillance program and website
- Evaluating existing data structures within the Virology Department to improve information transfer and reporting, and assisting in the analysis of the data within these databases
- Providing epidemiology guidance and training within the Virology Department

DoD Influenza Annual Meeting

AFIOH hosted the annual DoD Global Influenza Working Group meeting, 1-2 June, at Lackland AFB, TX. The meeting addressed a range of issues in influenza surveillance, covering the past season and preparations for the 2005-2006 season.

Attendees included representatives from:

- DoD-GEIS
- ASD-HA (Force Health Protection)
- AF/SGR (Modernization)
- CDC
- PACOM/SG
- AFRIMS (Bangkok, Thailand)
- NAMRU-2 (Jakarta, Indonesia)
- NAMRU-3, (Cairo, Egypt)
- Landstuhl RMC
- Naval Environmental Preventive Medicine Unit 7 (Sigonella, Italy)
- NHRC
- AFIOH

Presentations

In the past year, AFIOH has presented talks and/or posters at the following meetings:

- Force Health Protection Conference, Albuquerque, NM, August 2004
- Southwestern Association for Clinical Microbiology, San Antonio, TX, September 2004
- Syndromic Surveillance Conference, Boston, MA, November 2004
- The American Society of Tropical Medicine and Hygiene, Miami, FL, November 2004
- Vaccines and Related Biological Products Advisory Committee, Bethesda, MD, February 2005
- Armed Forces Epidemiological Board, Ft Dietrick, MD, March 2005
- IDGA Battlefield Healthcare Conference, Tyson's Corner, VA, March 2005
- Society of Armed Forces Medical Laboratory Scientists Conference, Jacksonville, FL, March 2005
- Armed Forces Infectious Disease Society, Honolulu HI, April 2005
- Asian-Pacific Military Medicine Conference, Hanoi, Vietnam, May 2005
- Clinical Virology Symposium, Clearwater Beach, FL, May 2005
- National Laboratory Response Network meeting, New Orleans, LA, May 2005
- American Society for Microbiology, Atlanta, Georgia, June 2005
- US-Mexico Border Health Association Influenza Workshop, Laredo, TX, June 2005

Recent Publications

Luke T. Daum, Michael Shaw, Alexander I. Klimov, Linda C. Canas, Elizabeth A. Macias, Debra Niemeyer, James P. Chambers, Robert Renthal, Sanjaya Kr. Shrestha, Ramesh Pd. Acharya, Shankar Pd. Huzdar, Nirmal Rimal, Khin Saw Myint, and Philip Gould. Influenza A (H3N2) Outbreak, Nepal. *Emerging Infectious Diseases.* 2005 Aug;11(8):1186-91.

Krafft AE, Russell KL, Hawksworth AW, McCall S, Irvine M, Daum LT, Connoly JL, Reid AH, Gaydos JC, Taubenberger JK. Evaluation of PCR testing of ethanol-fixed nasal swab specimens as an augmented surveillance strategy for influenza virus and adenovirus identification. *Journal of Clinical Microbiology.* 2005 Apr;43(4):1768-75.

Russell KL, Ryan MA, Hawksworth A, Freed NE, Irvine M, Daum LT; NHRC Respiratory Disease Surveillance Team. Effectiveness of the 2003-2004 influenza vaccine among US military basic trainees: a year of suboptimal match between vaccine and circulating strain. *Vaccine.* 2005 Mar 14;23(16):1981-5.

Daum LT, Ye K, Chambers JP, Santiago J, Hickman JR, Barnes WJ, Kruzelock RP, Atchley DH. Comparison of TaqMan and Epoch Dark Quenchers during real-time reverse transcription PCR. *Molecular & Cellular Probes.* 2004 June; 18 (3):207-9.

Blasiole DA, Metzgar D, Daum LT, Ryan MA, Wu J, Wills C, Le CT, Freed NE, Hansen CJ, Gray GC, Russell KL. Molecular analysis of adenovirus isolates from vaccinated and unvaccinated young adults. *Journal of Clinical Microbiology.* 2004 Apr; 42(4): 1686-93.

CONCLUSIONS

The primary goal of the DoD Global Influenza Surveillance Program is to prevent influenza outbreaks in military personnel due to emerging strains. Intermediate objectives include the identification and characterization of circulating strains of influenza viruses, the detection of variant strains of influenza due to antigenic changes (i.e., antigenic drift and shift), and the evaluation of influenza vaccine effectiveness. The program's contribution to VRBPAC is valued, as it impacts not only the health of the military, but of the world.

During the 2004-2005 influenza surveillance season, influenza A activity peaked in Week 3 (16–22 Jan 2005), while influenza B activity peaked during week 9 (27 Feb-7 Mar 2005). Of all processed specimens, 906 (33%) were positive for influenza viruses. Compared to last season when influenza B accounted for less than 1% of all influenza isolates identified, this season influenza B accounted for 19% of identified isolates. Of the influenza A viruses that were subtyped, 100% were H3N2, the majority of which were California-like variants. Influenza B viruses were found to be predominantly Shanghai (85%); 15% of influenza B samples were Hong Kong. The CDC preliminary data show similar patterns.

The success of the Program requires cooperation between clinical, laboratory, and public health/preventive medicine staff from all military branches. Continued awareness and participation is key to worldwide surveillance efforts and determination of the annual influenza vaccine composition.

Vaccine Information for the 2005–2006 Northern Hemisphere Influenza Season

The World Health Organization (WHO) has recommended that the 2005-2006 Northern Hemisphere influenza vaccine include A/California/7/2004(H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Shanghai/361/2002-like viruses. For the A/California/7/2004(H3N2)-like virus, US vaccine manufacturers will use the antigenically similar A/New York/55/2004 strain. For the B/Shanghai/361/2002-like virus, US vaccine manufacturers will include the antigenically similar B/Shanghai/361/2002, B/Jiangsu/10/2003, and B/Jilin/20/2003 strains. Information is available from the WHO at http://www.who.int/csr/disease/influenza/vaccinerecommendations1/en/.

Season summaries of the AFIOH portion of the DoD Global Influenza Surveillance Program may be downloaded from the Epidemiology Services Branch web page at https://afioh.brooks.af.mil/pestilence/Influenza/ or requested by phone at DSN 240-3471 COMM (210) 536-3471.

This project was supported in part by an appointment to the Research Participation Program at AFIOH administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and AFIOH.

FUTURE DIRECTIONS

During the annual meeting, the following issues were identified to help guide the future direction of the DoD Global Influenza Surveillance Program:

- Better contact with the sentinel sites to ensure they are contributing specimens to the Program
- Addition of the following sentinel sites: NH Bethesda, MD; Ft Drum, NY; NH Sigonella, Italy; Okinawa NH, Japan; JTF-Bravo exercise in Honduras. In addition, NAMRU-3 will establish surveillance at deployed sites in Kuwait
- The possibility of a comprehensive periodic influenza report that incorporates data from all GEIS-affiliated agencies, including AFIOH, NHRC, NAMRU-2, and NAMRU-3
- Further investigation into severe or fatal cases of pneumonia in which the standard testing done by laboratories were negative
- GEIS support towards Army efforts to better standardize influenza surveillance
- Standardization of lab procedures towards specimen collection and biosafety issues
- Further discussions on pandemic planning

In addition, as mentioned earlier, improvement of sentinel site participation is a priority for next season. To encourage better participation, AFIOH will generate a standardized protocol based on traditional sentinel site surveillance systems for monitoring participation rates. Activities covered by the protocol will include maintaining better and more frequent contact with site PHOs and MAJCOM public health offices toencourage sustained participation throughout the influenza season.

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APPENDIX A
AFIOH PARTNER SUMMARIES, 2004-05 INFLUENZA SEASON

Naval Health Research Center, San Diego, California

2004-05 Influenza Season Summary

CDR Kevin Russell, Anthony Hawskworth, Dave Metzgar, Marina Irvine and the NHRC Respiratory Illness Study Group

Naval Health Research Center (NHRC), San Diego, has been conducting population-based surveillance for febrile respiratory illness (FRI) at eight U.S. military basic training centers since 1998. During 2004-05, NHRC also conducted FRI surveillance among two other populations: military personnel aboard deployed ships and a civilian population near the U.S.-Mexico border. FRI is defined as an oral temperature of 100.5° F or greater and either cough or sore throat, as well as any case of radiologically confirmed nonbacterial pneumonia. Throat or nasal swab specimens are collected and shipped frozen to NHRC, where they undergo PCR testing for influenza A and adenovirus, and viral culture testing for influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza 1-3.

Among military basic trainees, 1,289 FRI cases were enrolled between 3 October 2004 and 31 March 2005. PCR and viral culture testing has shown that 43 (3.3%) were positive for influenza A (H3N2) and 4 (0.3%) were positive for influenza B. Seasonal results including vaccination status are shown in Fig.1. The impact of influenza upon recruit populations was similar to that seen during the previous 6 seasons (Fig. 2). Adenovirus remains the primary cause of FRI morbidity among recruits. See http://www.nhrc.navy.mil/geis/studies/febrile_respiratory_illness_surveillance.htm for more information on FRI surveillance among U.S. military trainees.

FRI surveillance was also conducted aboard 9 US Navy ships during 2004-05. Medical corpsmen aboard ships were given instruction and supplies to collect specimens and data from ill crewmembers. Seven of the ships have submitted specimens to date, and clusters of influenza A (H3N2) have been found aboard 6 different ships immediately following port stops. The most recent clusters occurred in late 2004 and early 2005 after port stops in Port Kalang, Malaysia, San Diego, CA, Astoria, OR, and Victoria, Canada.

Collaboration with the CDC's Border Infectious Disease Surveillance program during 2004-05 allowed us to conduct FRI surveillance at a civilian clinic in San Ysidro, CA. The clinic is a very short distance from the U.S.-Mexico border and serves a bi-national patient population. One hundred twenty one patients were enrolled between November 2004 and March 2005. Influenza A (H3N2) was identified in 7 (5.8%) of cases, and influenza B was found in 27 (22.3%) of cases in this largely unvaccinated population.

Hemagglutinin gene sequencing has been performed on influenza A isolates from all 3 patient populations mentioned above, and all isolates show sequences most similar to the California/7e/2004 (H3N2) strain. These isolates have been shared with CDC to augment their influenza repository.

Influenza Vaccine Effectiveness

Data from FRI surveillance was leveraged to estimate the effectiveness of the influenza vaccine among basic trainees during 2004-05. The vaccine was estimated to have been 86% effective in preventing laboratory-confirmed influenza in this population. We also concluded that both the inactivated influenza vaccine (injection) and the live, attenuated influenza vaccine (intranasal spray) were highly effective in preventing influenza infection.

Wild-Type Influenza versus Vaccine Strain

Increased use of live, attenuated influenza vaccine this season raised concern that recently-vaccinated patients might yield false positive influenza results due to shedding of the vaccine virus. We developed strain-specific PCR tests to distinguish between wild-type and vaccine strain influenza. Testing of potential false positives revealed that all influenza cases that we reported among recruits were indeed true infections.

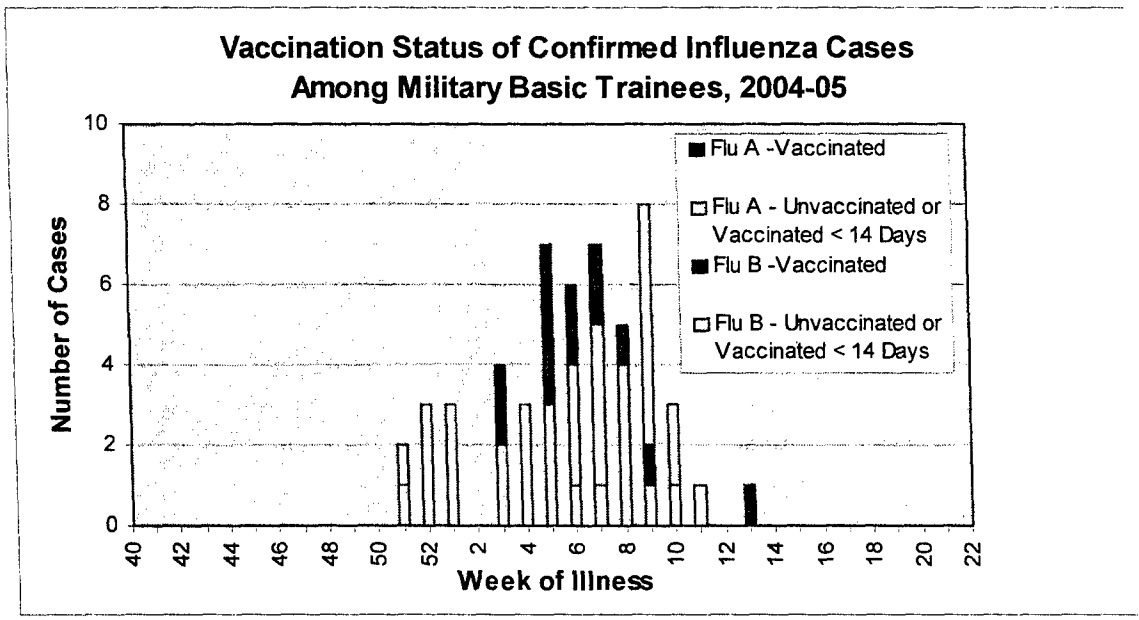


Figure 1. Vaccination Status of Confirmed Influenza Cases Among Military Basic Trainees, 2004-05

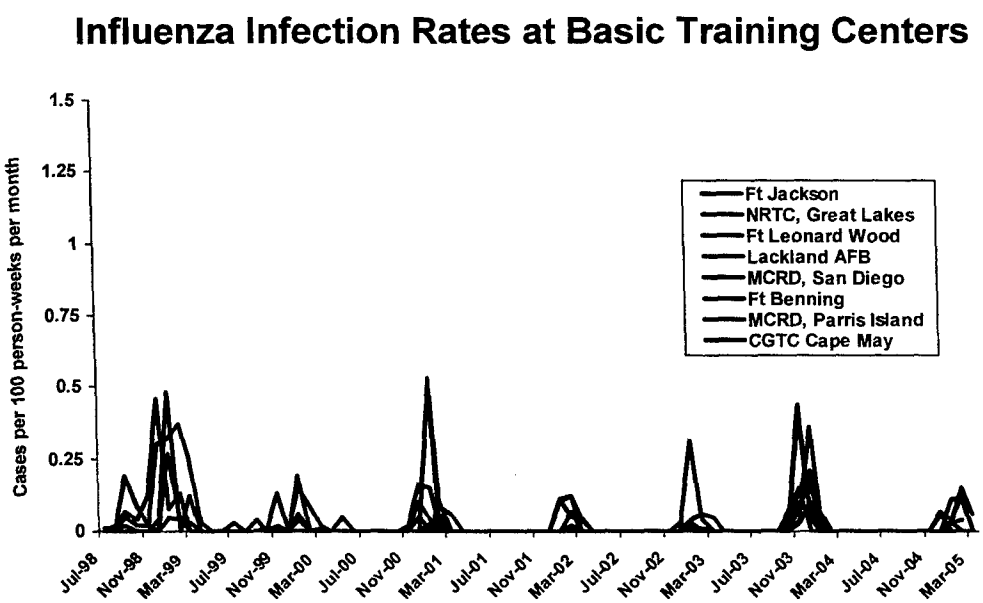


Figure 2. Influenza Infection Rates at Basic Training Centers

US Naval Medical Research Unit Two, Jakarta, Indonesia

2004-05 Summary, Southeast Asian Influenza Surveillance Initiative

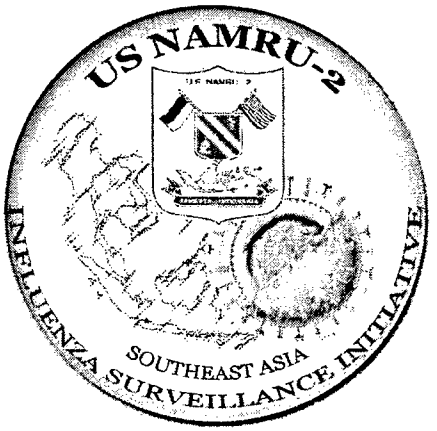
LCDR Patrick J. Blair, Director, Viral Diseases Program
LT Jonathan S. Glass, Director, Emerging Diseases Program

With support from DoD-GEIS, NAMRU-2 maintains the primary laboratory-based influenza surveillance program in Indonesia. In responses to the Avian Influenza (H5N1) crisis, NAMRU-2 investigators have now partnered with the US-CDC to expand influenza surveillance from six to twenty sites and utilized NAMRU-2's syndromic surveillance network which is deployed in four Southeast Asian countries – Laos, Cambodia, Indonesia, and Vietnam (32 sites).

Hospitals and clinics that best represent the geographic/ethical diversity of the nation have been enrolled. Specimens are collected from individuals with fever and influenza-like symptoms. Nasal and pharyngeal swabs are examined by polymerase chain reaction (PCR), and rapid immunochromatographic tests. Viruses are isolated and characterized if RT-PCR results for H5N1 are negative. Aliquots of viruses are shipped to either the WHO Collaborating Center for Influenza in Melbourne, Australia, or the US-CDC for molecularly identification. EWORS-

Between September 2004 and March 2005, 2,182 subjects reporting with an ILI were enrolled in the study, and 383 cases of influenza identified by RT-PCR. By isolation alone, 278 influenza viruses were characterized (overall isolation rate: 12.6%). Of these, 168 (60%) were Influenza A and 110 (40%) Influenza B viruses. To date, no human samples have proved positive for H5N1. No ILI outbreaks have been detected.

In Indonesia, this project has allowed for the most comprehensive assessment of influenza in the country while providing prevalence and information as to the genotypes of circulating viruses. Technology transfer and expansion of diagnostic capabilities to the Ministry of Health and Department of Agriculture has been a key component to this work.



The development of a comprehensive and geographically varied influenza surveillance program that provides comprehensive influenza surveillance over time is of particular importance in establishing the infrastructure to understand and respond to outbreaks of Avian Influenza in SE Asia.

Results from September 2004 to September 2005 will be presented at the 2005 ASTMH conference in Washington DC in December.

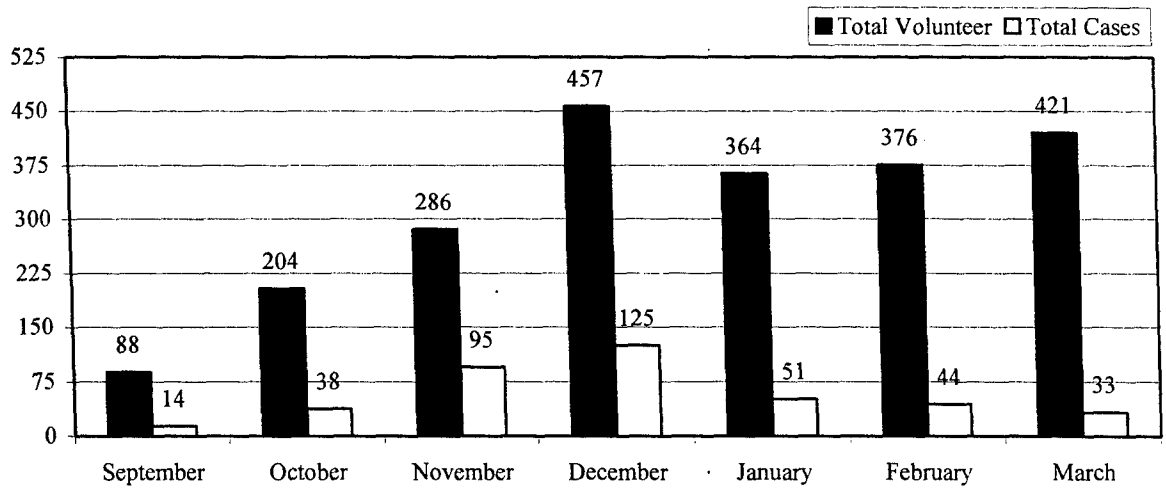


Figure 1. Number of participants/influenza cases* Sept 04-March 05, Indonesia.

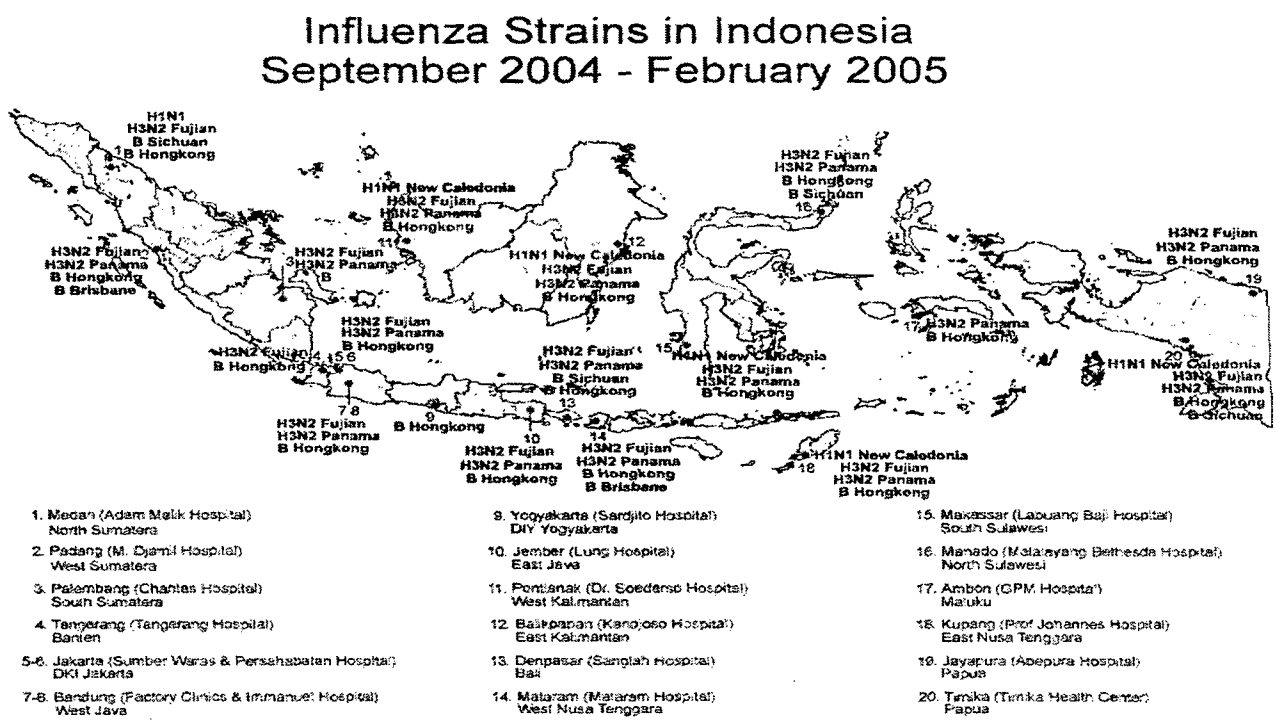


Figure 2. Geographical representation of viruses isolated

US Naval Medical Research Unit Three, Cairo, Egypt

2004-05 Influenza Season Summary

Capt(S) Ken Earhart, MAJ Sam Yingst, Dr. Diaa Elyan, Dr. Hala Esmat, Dr. Mike Parker and the Virology and Zoonotic Diseases Research Program

This year's Influenza A virus isolation results indicate pure circulation of H1N1 in Central Asia initially, followed by H3N2 viruses later. In terms of influenza A, only H3N2 circulated in Egypt, while Ukraine saw a mix of H1N1 and H3N2. Historically, Egypt has experienced trends similar to Europe and North America; this was the case again for this year. Central Asia had distinctive virus ecology when compared worldwide, illustrated by the isolation of only H1N1 viruses during a period that was dominated by isolation of H3N2 viruses elsewhere. Interestingly, Ukraine had a mix of H3N2 and H1N1 and may represent a crossroads between Central Asia and Europe/North America.

Selected viruses were further subtyped at CDC. Isolates from Kazakhstan and Kyrgyzstan were A/New Caledonia/20/99-like (H1N1). Influenza A viruses isolated between August-September in Egypt were A/California/07/2004-like (H3N2), whereas a later isolate was A/Wyoming/03/2003-like (H3N2) (one other isolate subtyped later was considered A/California-like, but the HAI results were equivocal with A/Wyoming-like). This again illustrates the parallel virus activity in Egypt to Europe and North America. Influenza B isolates from Egypt were all B/Shanghai/361/2002-like.

After 3-5 year collaborations, our collaborators in Egypt, Kazakhstan and Ukraine are now effectively independent National Influenza Centers. They solicit samples and isolates from sub-national laboratories, support them and coordinate their activities. They interact with WHO and neighboring nations to coordinate regional influenza surveillance. We will remain associated with them as a reference lab only.

Newer collaborations will take time to mature. In some cases, we are aiding the establishment of new national influenza centers, while in others we are helping recognized national influenza centers to resume thorough surveillance. We are confident that the new national influenza centers we have helped establish in Kyrgyzstan, Uzbekistan, Syria, Oman, and Saudi Arabia will soon be fully functioning and WHO-recognized. We have assisted the National Influenza Center of Kenya with resuming influenza surveillance by providing training, supplies and reagents, and establishing a protocol for sample collection in collaboration with USAMRU-K. We are similarly assisting the national influenza center of Pakistan. We also assist the national influenza center of Morocco with surge capacity.

TABLE 1. Influenza isolation at NAMRU-3 or by NAMRU-3 collaborators 2004 – 2005 Influenza Season.

	Samples Collected	Influenza A H1 (% +)	Influenza A H3 (% +)	Influenza B (% +)	Influenza not sub-typed (% +)	Negative (%)
Kyrgyzstan	114	17	0	0	8	28
Kazakhstan	167	12	1	5	28	62
Egypt	2,644	0	41	252	121	2,093
Ukraine	251	8	3	85	45	106

So far in the '04-'05 season, 5 migratory bird isolates have been obtained from Egypt. These viruses are not reactive to antisera to H1,3,5,6,7, or 9. Therefore, these viruses probably represent avian viruses not pathogenic for chickens or humans. One isolate was identified as an H1 by sequencing and 3 of the 5 have the N7 neuraminidase. Sequencing will continue.

TABLE 2. Migratory Bird Results			
	Virus Isolations	RT-PCR +	Total
ABU SIMBEL	2	6	102
DOMIATTA	3	79	534
FAYOUM	0	7	66
		92	702

APPENDIX B
SUPPLEMENTARY TABLES

TABLE B1. Sentinel Site List*†

CONUS			
Installation	**Location**	**Installation**	**Location**
Andrews AFB	Maryland	NMC San Diego	California
Maxwell AFB	Alabama	Scott AFB	Illinois
McGuire AFB	New Jersey	Sheppard AFB	Texas
NAB Little Creek	Virginia	Travis AFB	California
NH Bremerton	Washington	USAF Academy	Colorado

EUCOM			
Installation	**Location**	**Installation**	**Location**
Aviano AB	Italy	Landstuhl RMC	Germany
BMC Sasebo	Japan	RAF Lakenheath	United Kingdom
Incirlik AB	Turkey	Ramstein AB	Germany

PACOM			
Installation	**Location**	**Installation**	**Location**
Andersen AFB	Guam	NH	Guam
CGS Ketchikan	Alaska	NH Pearl Harbor	Hawaii
Elmendorf AFB	Alaska	Osan AB	Korea
Hickam AFB	Hawaii	Pearl Harbor NS	Hawaii
Kadena AB	Japan	Tripler AMC	Hawaii
Kunsan AB	Korea	Yokosuka NH	Japan
Misawa AB	Japan	Yokota AB	Japan

CENTCOM			
Installation	**Location**	**Installation**	**Location**
Al Udeid AB	Qatar	Ganci AB	Kyrgrystan

* Hickam AFB and NH Pearl Harbor submit specimens through Tripler AMC, HI

† NH, Guam submits specimens through Anderson AB, Guam

TABLE B2. Respiratory Isolates by Site Type

Virus	Sentinel		Non-Sentinel		Overseas	
	N	%	N	%	N	%
Influenza A	531	(29)	151	(23)	53	(18)
Influenza B	136	(7)	21	(3)	14	(5)
Parainfluenza	13	(1)	8	(1)	5	(2)
Adenovirus	50	(3)	40	(6)	7	(2)
Enterovirus	4	(0)	3	(1)	3	(1)
Herpes Simplex	13	(1)	13	(2)	6	(2)
RSV	2	(0)	2	(0)	1	(0)
No virus isolated	1060	(59)	425	(64)	211	(70)

TABLE B3. Influenza Isolates by Site Type

Virus	Sentinel		Non-Sentinel		Overseas	
	N	%	N	%	N	%
Influenza A	531	(80)	151	(85)	53	(79)
Influenza B	136	(20)	21	(15)	14	(21)

TABLE B4. Number and Percentage of Isolates by CDC Geographical Region*

Region	Influenza A		Influenza B		Parainfluenza		Adenovirus		Enterovirus		HSV		RSV		No Virus	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
New England	1	(100)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Mid Atlantic	71	(46)	12	(8)	2	(1)	3	(2)	0	(0)	1	(1)	0	(0)	64	(42)
East North Central	58	(14)	19	(5)	6	(1)	26	(6)	0	(0)	1	(0)	2	(0)	311	(74)
West North Central	3	(7)	1	(2)	2	(4)	1	(2)	0	(0)	2	(4)	2	(4)	35	(76)
South Atlantic	33	(26)	18	(14)	1	(1)	3	(2)	0	(0)	1	(1)	0	(0)	72	(56)
East South Central	57	(38)	7	(5)	0	(0)	1	(1)	0	(0)	3	(2)	0	(0)	79	(54)
West South Central	95	(16)	9	(2)	3	(0)	41	(7)	6	(1)	8	(1)	0	(0)	433	(73)
Mountain	47	(47)	7	(7)	0	(0)	3	(3)	0	(0)	1	(1)	0	(0)	42	(42)
Pacific	51	(29)	42	(24)	1	(1)	2	(1)	0	(0)	6	(3)	0	(0)	75	(42)
Pacific Rim	46	(22)	30	(15)	2	(1)	4	(2)	1	(0)	1	(0)	0	(0)	121	(59)
Europe	203	(44)	12	(3)	4	(1)	6	(1)	0	(0)	2	(0)	0	(0)	232	(51)
South America	53	(18)	14	(5)	5	(2)	7	(2)	3	(1)	6	(2)	1	(0)	212	(70)
Deployed	17	(46)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	20	(54)

* According to CDC Region definitions, Hawaii sites were placed in the Pacific (CONUS) region rather than with Asian sites as was done earlier in this report

TABLE B5. Number and Percentage of Isolates by Age Group

Age Group	Influenza A		Influenza B		Parainfluenza		Adenovirus		Enterovirus		HSV		RSV		No Virus	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0-5	59	(9)	31	(20)	15	(65)	36	(40)	4	(40)	6	(19)	3	(60)	382	(24)
6-17	122	(18)	47	(30)	1	(5)	12	(13)	1	(10)	5	(16)	1	(20)	254	(16)
18-55	445	(68)	72	(46)	7	(30)	43	(47)	5	(50)	18	(58)	1	(20)	872	(55)
56 and over	32	(5)	7	(4)	0	(0)	0	(0)	0	(0)	2	(7)	0	(0)	80	(5)

TABLE B6. Number and Percentage of Isolates by FMP Status

FMP Status	Influenza A		Influenza B		Parainfluenza		Adenovirus		Enterovirus		HSV		RSV		No Virus	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Active Duty	381	(52)	54	(32)	3	(12)	39	(40)	5	(50)	16	(50)	0	(0)	733	(43)
Family Member	258	(35)	99	(58)	18	(69)	50	(52)	2	(20)	9	(28)	4	(80)	737	(43)
Overseas Research	93	(13)	17	(10)	5	(19)	7	(7)	3	(30)	6	(19)	1	(20)	213	(13)
Other	3	(0)	1	(0)	0	(0)	1	(1)	0	(0)	1	(3)	0	(0)	14	(1)